UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,926	05/03/2007	Barbara Ensoli	114-06	7925

23713 7590 03/13/2012

GREENLEE SULLIVAN P.C.
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
03/13/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,926	ENSOLI, BARBARA	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *35-50,52-56 and 63-72* is/are pending in the application.

5a) Of the above claim(s) *53-56 and 65-67* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *35-50,52,63,64 and 68-72* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections

The rejection of claims 42, 47, 69 and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicant's amendments to the claims.

The rejection of claims 42, 47, 69 and 71 under 35 U.S.C. 112, second paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicant's amendments to the claims.

Claim Objections

Claim 50 is objected to because of the following informalities: Claim 50 should recite "is selected from" after the phrase "wherein the Tat fragment." Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-50, 52, 63, 64 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. (WO 01/54719) and further in view of Caselli et al. (J.

Immunol., 1999, 162:5631-5638), Chang et al. (Vaccine, 1999, 17:1540-1548), Borbe et al. (Journal of Peptide Science, 1995, 1:109-123), Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al. (Virus Research, 1999, 60:159-169) and Watanabe et al. (Vaccine, 2000, 19(9-10):1199-1203).

The claims are directed to a complex comprising a first and a second peptide bound thereto, the first peptide comprising the V3 loop of gp120, and wherein the V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex, said second peptide comprising the binding region which region comprises at least residues 21-40 and 46-58 of the Tat protein set forth in SEQ ID NO:1, or at least said residues with a further point mutation whereby Cys22 of Tat is replaced by Glycine to form a Tat22Cys22 mutant, said Tat protein binding a region on gp120 comprising residues 301-419 of a gp120 protein as set forth in SEQ ID NO:2.

The instant claims do not require any particular bond to hold the complex components together. According to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. Whilst it is preferred, it is not necessary that the two species be present in stoichiometric amounts, nor that even a majority of either species be complexed or bound to the other. All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Page 5 of the specification further states that "The complex of the present invention may rely simply on the natural interaction between Tat and the V3 loop of gp120. Weaker complexes may also be employed, but it is generally preferred to strengthen the complex. In this respect, for example, it is possible to employ the disulphide bridges that can occur in association with the cysteine-reach region of the Tat protein, or to use other protein cross-linking technologies that are known in the art such as, for example, the BS3 cross-linker." (emphasis added)

Voss et al. discloses the use of an HIV Tat protein and an HIV gp120 protein in the manufacture of a vaccine for immunization against HIV (abstract). In accordance with the teaching in the instant specification, Voss et al. discloses a combination of the two proteins, and a complex that relies simply on the natural interaction between Tat and the V3 loop of gp120 will form between the two proteins. Voss also discloses a kit comprising one or more of gp120, Nef and Tat proteins (see page 12).

Voss et al. does not teach the use of a Cys22 Tat mutant, the use of the V3 loop as the first peptide (claim 41), gp120 V2 deletion mutants (claims 43 and 44), the addition of CD4 to the complex (claims 46 and 47), the addition of heparin sulphate to the complex (claim 48), the addition of other immune proteins (claim 49) or cross-linking the peptides (claim 52).

Caselli et al. teaches the use of Cys22 Tat mutants as immunogens. Caselli et al. teaches that because of the possible use of Tat as a component of an anti-HIV-1 vaccine (prophylactic and/or therapeutic) and considering the possibility that the long term expression and release of wild-type Tat in vivo may reactivate HIV-1 expression,

Tat mutants that lack the ability to transactivate the HIV promoter (e.g., Cyss22 to Gly mutants) are good vaccine candidates (see page 5632). Caselli et al. found that the Tat mutants induced broad humoral and cellular responses (see, for example, the abstract and page 5632).

It would have been obvious to one of ordinary skill in the art to modify the immunogenic complex taught Voss et al. and use a Tat Cys22 mutant. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings and findings of Caselli et al. (if Tat is to be used as a vaccine, it should be mutated to eliminate the transactivation property while still maintaining the ability to induce immune responses).

It is well known in the art that the V3 loop is one of the most immunogenic peptides/fragments of gp120 (see, for example, Chang et al. and Borbe et al.). Thus, it would have been obvious to one of ordinary skill in the art to produce the vaccine composition of Voss et al. using Tat and known HIV Env proteins comprising the V3 loop of HIV (e.g., gp120, gp145 or gp160) or consisting of the V3 loop of HIV gp120. One would have been motivated to do so and there would have been a reasonable expectation of success as both proteins are known in the art as immunogenic and HIV vaccine candidates. It also would have been obvious to cross-link the gp120 and Tat as cross-linking of vaccine antigens is common (see, for example, Watanabe et al.).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of

cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it also would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Voss et al. One would have been motivated to do so and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells, which would cause the exposure of gp120 epitopes.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or

other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

In the reply dated January 3, 2012, applicant argues that although the prior art discloses Tat and gp120 together, in the absence of the exposure of the binding residues of the V3 loop, the only interaction that exists between the two proteins are Van der Waals forces. Applicant's arguments have been fully considered but not found persuasive.

As outlined above, the specification defines the complex as relying simply on the natural interaction between Tat and the V3 loop of gp120, and the claim does not define a particular bond between the proteins to create the complex. Thus, Voss et al. meets the limitations of the claims.

Applicant next argues that specific forms of gp120 (trimeric Env, trimeric ΔV2 Env and monomeric ΔV2 Env) are required to expose the V3 loop and form complexes with Tat. In support of this argument, applicant provided two references, Gorny and Fouts. It is noted that the claims are not limited to these forms of Env. As written, the

claims include monomeric gp120. Further, the specification states that complex formation can rely on the natural interaction of gp120 and Tat. In addition, because the complex of Voss et al. is structurally the same as the instantly claimed complex, the V3 loop of gp120 in the complex of Voss et al. was exposed and bound by Tat at residues 301-419.

Applicant next argues that secondary references Gyzl and Wyatt do not teach or suggest that Tat mimics the CCR5 receptor or that Tat binds gp120 via the V3 loop. Applicant also argues that secondary references Sattenau and Ibrahim provide no motivation for exposing the V3 loop. These features are inherent properties of the Voss et al. complex that naturally forms between Tat and gp120. As outlined above, the specification defines the complex as relying simply on the natural interaction between Tat and the V3 loop of gp120, and the claim does not define a particular bond between the proteins to create the complex. The complex of Voss et al. meets the limitations of the claims. Thus, because the complex can form due to the natural interaction of Tat and gp120, the V3 loop of gp120 was exposed and bound to Tat.

Claims 35-50, 52, 63, 64 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. (Journal of Virology, 2003, 77(2):1049-1058) and further in view of Caselli et al. (J. Immunol., 1999, 162:5631-5638), Chang et al. (Vaccine, 1999, 17:1540-1548), Borbe et al. (Journal of Peptide Science, 1995, 1:109-123), Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al.

(Virus Research, 1999, 60:159-169) and Watanabe et al. (Vaccine, 2000, 19(9-10):1199-1203).

The claims are directed to a complex comprising a first and a second peptide bound thereto, the first peptide comprising the V3 loop of gp120, and wherein the V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex, second peptide comprising the binding region which region comprises at least residues 21-40 and 46-58 of the Tat protein set forth in SEQ ID NO:1, or at least said residues with a further point mutation whereby Cys22 of Tat is replaced by Glycine to form a Tat22Cys22 mutant being capable of binding a region on gp120 comprising residues 301-419 of SEQ ID NO:2.

The instant claims do not recite the type of bond holding the complex components together. However, according to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. Whilst it is preferred, it is not necessary that the two species be present in stoichiometric amounts, nor that even a majority of either species be complexed or bound to the other. All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Page 5 of the specification further states that "The complex of the present invention may rely simply on the natural interaction between Tat and the V3 loop of

gp120. Weaker complexes may also be employed, but it is generally preferred to strengthen the complex. In this respect, for example, it is possible to employ the disulphide bridges that can occur in association with the cysteine-reach region of the Tat protein, or to use other protein cross-linking technologies that are known in the art such as, for example, the BS3 cross-linker." (emphasis added)

Voss et al. discloses the use of an HIV Tat protein and an HIV gp120 protein in the manufacture of a vaccine for immunization against HIV (abstract). In accordance with the teaching in the specification, Voss et al. discloses a combination of the two proteins, and a complex that relies simply on the natural interaction between Tat and the V3 loop of gp120 will form between the two proteins. Voss also discloses a kit comprising one or more of gp120, Nef and Tat proteins (see page 12).

Voss et al. does not teach use of a Cys22 Tat mutant, the use of the V3 loop as the first peptide (claim 41), gp120 V2 deletion mutants (claims 43 and 44), the addition of CD4 to the complex (claims 46 and 47), the addition of heparan sulphate to the complex (claim 48), the addition of other immune proteins (claim 49) or cross-linking the peptides (claim 52).

Caselli et al. teaches the use of Cys22 Tat mutants as immunogens. Caselli et al. teaches that because of the possible use of Tat as a component of an anti-HIV-1 vaccine (prophylactic and/or therapeutic) and considering the possibility that the long term expression and release of wild-type Tat in vivo may reactivate HIV-1 expression, Tat mutants that lack the ability to transactivate the HIV promoter (e.g., Cyss22 to Gly mutants) are good vaccine candidates (see page 5632). Caselli et al. found that the Tat

mutants induced broad humoral and cellular responses (see, for example, the abstract and page 5632).

It would have been obvious to one of ordinary skill in the art to modify the immunogenic complex taught Voss et al. and use a Tat Cys22 mutant. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings and findings of Caselli et al. (if Tat is to be used as a vaccine, it should be mutated to eliminate the transactivation property while still maintaining the ability to induce immune responses).

It is well known in the art that the V3 loop is one of the most immunogenic peptides/fragments of gp120 (see, for example, Chang et al. and Borbe et al.). Thus, it would have been obvious to one of ordinary skill in the art to produce the vaccine composition of Voss et al. using Tat and known HIV Env proteins comprising the V3 loop of HIV (e.g., gp120, gp145 or gp160) or consisting of the V3 loop of HIV gp120. One would have been motivated to do so and there would have been a reasonable expectation of success as both proteins are known in the art as immunogenic and HIV vaccine candidates. It also would have been obvious to cross-link the gp120 and Tat as cross-linking of vaccine antigens is common (see, for example, Watanabe et al.).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding.

Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it also would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Voss et al. One would have been motivated to do so and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells, which would cause the exposure of gp120 epitopes.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the

immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

In the reply dated January 3, 2012, applicant argues that although the prior art discloses Tat and gp120 together, in the absence of the exposure of the binding residues of the V3 loop, the only interaction that exists between the two proteins are Van der Waals forces. Applicant's arguments have been fully considered but not found persuasive.

As outlined above, the specification defines the complex as relying simply on the natural interaction between Tat and the V3 loop of gp120, and the claim does not define a particular bond between the proteins to create the complex. Thus, Voss et al. meets the limitations of the claims.

Applicant next argues that specific forms of gp120 (trimeric Env, trimeric ΔV2 Env and monomeric ΔV2 Env) are required to expose the V3 loop and form complexes with Tat. In support of this argument, applicant provided two references, Gorny and Fouts. It is noted that the claims are not limited to these forms of Env. As written, the claims include monomeric gp120. Further, the specification states that complex formation can rely on the natural interaction of gp120 and Tat. In addition, because the

complex of Voss et al. is structurally the same as the instantly claimed complex, the V3 loop of the complex of Voss et al. was exposed and bound by Tat at residues 301-419.

Applicant next argues that secondary references Gyzl and Wyatt do not teach or suggest that Tat mimics the CCR5 receptor or that Tat binds gp120 via the V3 loop. Applicant also argues that secondary references Sattenau and Ibrahim provide no motivation for exposing the V3 loop. These features are inherent properties of the Voss et al. complex that naturally forms between Tat and gp120. As outlined above, the specification defines the complex as relying simply on the natural interaction between Tat and the V3 loop of gp120, and the claim does not define a particular bond between the proteins to create the complex. The complex of Voss et al. meets the limitations of the claims. Thus, because the complex can form due to the natural interaction of Tat and gp120, the V3 loop of gp120 was exposed and bound to Tat.

Claims 35-50, 52, 63, 64 and 68-72 are rejected under 35 U.S.C. 103(a) unpatentable over Debrus et al. (WO 02/087614) and further in view of Caselli et al. (J. Immunol., 1999, 162:5631-5638), Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al. (Virus Research, 1999, 60:159-169).

Debrus et al. discloses a vaccine composed of HIV-1 gp120 and Nef-Tat fusions or Nef and Tat. Debrus et al. teaches that the gp120 protein is the principal target of neutralizing antibodies, but unfortunately the most immunogenic regions of the proteins (V3 loop) are also the most variable parts of the protein. Therefore, the use of gp120

(or its precursor gp160) alone as a vaccine antigen to elicit neutralizing antibodies is thought to be of limited use for a broadly protective vaccine. The gp120 protein does also contain epitopes that are recognized by cytotoxic T lymphocytes (CTL). For this reason gp120 and gp160 are considered to be useful antigenic components in vaccines that aim at eliciting cell-mediated immune responses (particularly CTL). Non-envelope proteins of HIV-1 have been described and include for example internal structural proteins such as the products of the gag and pol genes and, other non-structural proteins such as Rev, Nef, Vif and Tat (see pages 1 and 2).

Debrus et al. also teaches preferred combinations of adjuvant and antigen comprise the HIV gp120 and Nef-Tat proteins in combination with QS2 1,3D-MPL in an oil in water emulsion and that the proteins can be cross-linked. Preferably the Tat, Nef or Nef-Tat act in synergy with gp120 in the treatment or prevention of HIV (see pages 14 and 17).

In accordance with the teaching in the specification (see page 5 of the specification), Debrus et al. discloses a combination of the two HIV proteins, and a complex will form between the two proteins that relies simply on the natural interaction between Tat and the V3 loop of gp120.

Debrus et al. does not teach use of a Cys22 Tat mutant, the use of the V3 loop as the first peptide (claim 41), gp120 V2 deletion mutants (claims 43 and 44), the addition of CD4 to the complex (claims 46 and 47), the addition of heparin sulphate to the complex (claim 48), the addition of other immune proteins (claim 49) or cross-linking the peptides (claim 52).

Caselli et al. teaches the use of Cys22 Tat mutants as immunogens. Caselli et al. teaches that because of the possible use of Tat as a component of an anti-HIV-1 vaccine (prophylactic and/or therapeutic) and considering the possibility that the long term expression and release of wild-type Tat in vivo may reactivate HIV-1 expression, Tat mutants that lack the ability to transactivate the HIV promoter (e.g., Cyss22 to Gly mutants) are good vaccine candidates (see page 5632). Caselli et al. found that the Tat mutants induced broad humoral and cellular responses (see, for example, the abstract and page 5632).

It would have been obvious to one of ordinary skill in the art to modify the immunogenic complex taught Voss et al. and use a Tat Cys22 mutant. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings and findings of Caselli et al. (if Tat is to be used as a vaccine, it should be mutated to eliminate the transactivation property while still maintaining the ability to induce immune responses).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Debrus et al. One would have been motivated and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells, which would cause the exposure of gp120 epitopes.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4, heparan sulphate or other similar acting components/receptors (e.g., integrins, basic fibroblast growth factor, CD26, VEGF receptors, and chemokine receptors) that would further expose the immunogenic peptides/epitopes of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV. One would be motivated to do so and

there would be a reasonable expectation of success as V3 is known in the art as immunogenic, as a vaccine candidate and as inducing neutralizing antibodies.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated January 3, 2012, applicant again argues that none of the cited references teach the necessity for the accessibility of the V3 loop nor do any of the references teach conditions which would make the V3 loop available for binding to Tat. Applicant's arguments have been fully considered but not found persuasive.

As noted above, the instant claims do not require any particular type of bond between the complex components Tat and gp120 V3. However, according to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. . . . All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Page 5 of the specification further states that "The complex of the present invention may rely simply on the natural interaction between Tat and the V3 loop of gp120. Weaker complexes may also be employed, but it is generally preferred to strengthen the complex. In this respect, for example, it is possible to employ the disulphide bridges that can occur in association with the cysteine-reach region of the

Tat protein, or to use other protein cross-linking technologies that are known in the art such as, for example, the BS3 cross-linker." (emphasis added)

The cited references teach immunogenic compositions comprising Tat and gp120 with an intact V3 loop. Therefore, according to the teachings of the specification, Tat and V3 of gp120 will naturally interact and form a complex.

This is an inherent feature of the prior art Tat/gp120 compositions, and according to §2112(II) of the M.P.E.P., there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.").

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B. Chen/
Primary Examiner, Art Unit 1648